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Communication

Unexpected Formation of Oxetanes during the Synthesis of Dodeco-6,7-diuloses

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Abstract: During the synthesis of symmetrical dodeco-6,7-diuloses that are potential candidates for inhibition of glycosidases, an unanticipated epoxide-oxetane rearrangement was observed. A bicyclic sugar consisting of a glycal moiety and an anomeric esterified furanose was oxidized under epoxidation conditions (*m*CPBA/KF). The isolation of the pure epoxide was not possible since a rapid reversible conversion accompanied by the migration of the ester group took place and resulted in the formation of an unusual oxetane-bridged disaccharide scaffold. X-ray diffractometric structure elucidation and the suggested mechanism of the rearrangement are provided.

Keywords: oxetane; epoxide; rearrangement; carbohydrate; *C*-glycosylation; spiro-oxetane; ester group migration

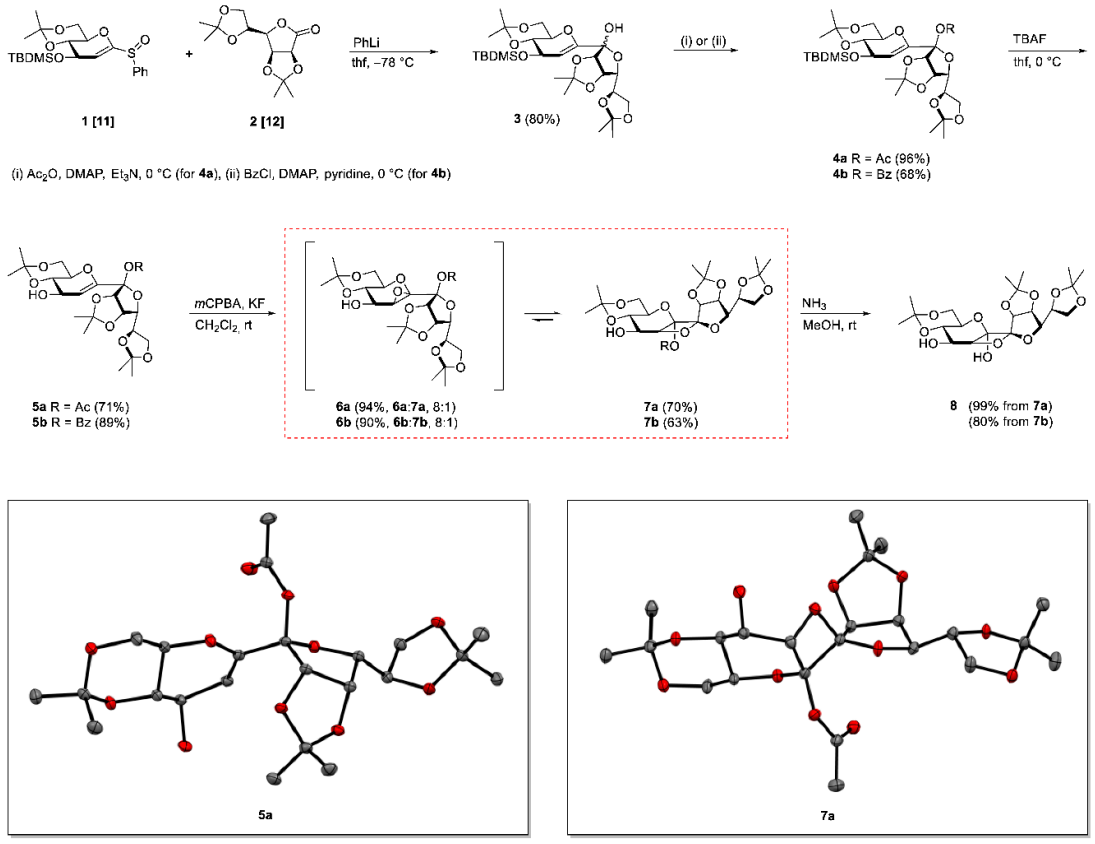
1. Introduction

Oxetane rings attached directly to a carbohydrate unit rarely occur in literature, due to steric reasons [1]. The most common representatives are 3,5-anhydrofuranose derivatives, which are formed by nucleophilic [2,3] or additive [4] intramolecular ring closure reactions. In addition to the furanoid 3,5-linked oxetanes, there also exists a limited number of 1,2-fused or anomeric spiro-oxetanes having a pyranoid constitution. These highly strained scaffolds are prepared photochemically [5–7] or via template-directing *C*-glycosylations [8,9]. In synthesis, sugar oxetanes are used as versatile precursors since the rigid conformation and steric repulsion of the bridge favor high stereoselectivities [10]. Furthermore, the detection of antimicrobial properties has brought these structures closer to the focus of current research [4]. In this communication, we introduce a new method for the generation of anomerically bridged oxetanes whose formation was initiated by an unexpected rearrangement of an epoxide assisted by an adjacent ester group.

2. Results and Discussion

Starting from the known compounds **1** [11] and **2** [12] a base-induced coupling of two anomeric centers analogous to Shiozaki's protocol [13] was performed (Scheme 1). Contrary to Shiozaki's procedure, which involved the use of toxic stannylated glycals, we could employ 1-phenylsulfinyl glycals since it is known that they are easily lithiated in a similar fashion with one equivalent of phenyllithium [14]. Sulfoxide 1 was treated with phenyllithium at –78 °C followed by quenching with *manno*-lactone 2 after 5 minutes. The observance of this reaction time is mandatory since a longer reaction time results in the irreversible formation of the protonated glycal species in increasing amounts leading to by-products. The coupled disaccharide 3 was isolated as an anomeric mixture (α/β ratio 1:5) in 80% yield. Next, the anomeric hydroxyl group was masked in order to avoid its coordinating effect on the envisaged stereoselective epoxidation. For this purpose, we decided to

choose the ester protecting groups acetyl and benzoyl. Thus, the fully protected disaccharides **4a** and **4b** were obtained after the acylation step in 96% and 68% yield, respectively. In both cases solely the β-anomers were obtained which was proven by H,H-NOESY NMR spectroscopy (see Supplementary Materials).



Scheme 1. Synthesis of the isopropylidene-protected oxetane-bridged disaccharide **8** and X-ray structures of **5a** and **7a**.

Furthermore, the configuration could be confirmed by growing crystals of **5a** suitable for X-ray diffraction by recrystallization of the latter from *n*-hexane and ethyl acetate. Compound **5a** was obtained through desilylation of **4a** with tetra-*n*-butylammonium fluoride (Scheme 1). The moderate yield of 71% can be explained by detectable partial cleavage of the acetyl group in alkaline milieu during desilylation. The benzoyl protecting group was significantly more stable under the same conditions resulting in a yield of 89% for the conversion of **4b** to **5b**. In our efforts to synthesize symmetrical dodeco-6,7-diuloses both sugar moieties need to be *manno*-configured. Therefore, the next step was to stereoselectively convert the glycal entity into a mannose derivative. Conventional methods for the implementation of stereoselective dihydroxylation on similar allyl alcohol systems use substrate-directing reagents such as molybdenum catalysts [15], vanadyl acetylacetonate ($VO(acac)_2$) [16,17] or *meta*-chloroperbenzoic acid (*m*CPBA) [17,18] for epoxidation. Subsequent epoxide opening leads to the desired diol derivatives. When these methodologies were applied to disaccharides **5a** and **5b** the best results were achieved using the Camps reagent (*m*CPBA/KF) [18,19]. The addition of potassium fluoride reduces the solubility of *m*CPBA and *m*CBA and thus, inhibiting nucleophilic epoxide opening by the acids. However, we could not isolate the pure epoxides **6a** and **6b** for a rapid rearrangement of the latter to oxetane species **7a** and **7b** occurred. Upon early quenching of the epoxidation reaction, only 8:1 mixtures of epoxide and oxetane could be isolated in yields of 94% for **6a** and 90% for **6b**, respectively. In order to enable the complete conversion of the epoxide to the oxetane derivatives the reaction times were extended and **7a** and **7b** could be obtained

neatly in 70% and 63% yields, respectively. Crystals of compound **7a** suitable for X-ray crystallography could be obtained by overlaying a saturated solution of **7a** in methylene chloride with *n*-heptane and slowly evaporating the methylene chloride. Thus, the oxetane-bridged disaccharide structure of **7a** with two anomeric *α*-configurations could be unambiguously verified (Scheme 1). For the formation of oxetanes **7** we propose a mechanism deduced from the X-ray data in which ester group migration from position 7 to 6 occurs simultaneously with *O*-heterocyclic ring extension of the oxirane ring to the less strained oxetane ring (Figure 1). The rearrangement process can also be visualized by ^{1}H-NMR spectroscopy since the H-5 signal of oxetane **7a** (4.96 ppm, 4.6 Hz) is significantly shifted to lower field compared to the characteristic doublet of H-5 in epoxide **6a** (3.66 ppm, 2.4 Hz) (Figure 1). To some extent, this rearrangement resembles the Ferrier rearrangement of acetylated glycals. Alternatively, a stepwise mechanism via the intermediate formation of carbenium ions can also be envisaged.

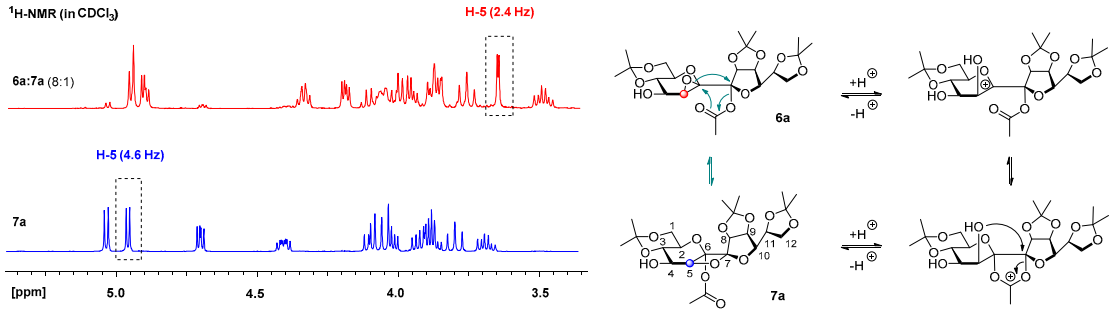


Figure 1. Proposed mechanisms for the rearrangement from epoxide **6a** to oxetane **7a** and their ^{1}H-NMR spectra in $CDCl_3$ to illustrating the reaction progress.

It must also be mentioned that the rearrangement appeared to be reversible for in attempts to recrystallize **7a** from boiling *n*-hexane the precipitation of an amorphous substance which turned out to be epoxide **6a** was observed. Studies are ongoing to evaluate both the effect of the temperature and of the solvent on the equilibrium ratio between compounds **6a** and **7a**. After removal of the ester protecting groups of **7a** and **7b** with ammonia in methanol, oxetane **8** was obtained from both compounds in 99% and 80% yield respectively (Scheme 1). Oxetanes **8** did not recede to the corresponding epoxides according to TLC monitoring. Consequently, it was proven that **7b** is also present as an oxetane-fused disaccharide.

3. Materials and Methods

All reactions were performed under an atmosphere of nitrogen using solvents dried by standard procedures. Reaction progress was monitored by TLC on Polygram SIL G/UV$_{254}$ silica gel plates from Macherey and Nagel, Germany. Detection of spots was affected by carbonizing with sulfuric acid (5% in EtOH), staining by spraying the plates with an alkaline aqueous solution of potassium permanganate or by inspection of the TLC plates under UV light (254 nm). Preparative flash chromatography was performed on silica gel (0.032–0.063 mm) from Macherey-Nagel, using plastic cartridges from Götec. The flowrate was regulated by a Sykam S1122 solvent delivery system. Nuclear magnetic resonance (NMR) spectra were recorded with a Bruker Avance 400 spectrometer and calibrated for the solvent signal (^{1}H: $CDCl_3$: δ = 7.26 ppm; acetone-d_6: δ = 2.05 ppm; DMSO-d_6: δ = 2.50 ppm; ^{13}C: $CDCl_3$: δ =77.16 ppm; acetone-d_6: δ = 29.92 ppm; DMSO-d_6: δ = 39.52 ppm). All NMR-assignments were proven by 2D-experiments to be correct. ESI-TOF-HRM spectrometry was performed on a Bruker MAXIS 4G spectrometer. Elemental analyses were obtained from a HEKA tech Euro EA 3000 apparatus. Optical rotations were determined with a Perkin-Elmer Polarimeter 341 in a 10 cm cuvette at 20 °C with a wavelength of 589 nm (Na-lamp). Melting points were measured with a Büchi Melting Point M-560 apparatus.

2,6-Anhydro-5-deoxy-4-O-(tert-butyldimethylsilyl)-1,3:8,9:11,12-tri-O-isopropylidene-D-arabino-L-gulo-dodeco-7-ulo-6-enitol (**3**)

To a suspension of **1** (2.62 g, 6.18 mmol) and grounded molecular sieve (3 Å, 30 mg) in THF (40 mL) was added phenyllithium (1.9 M in Bu_2O, 3.57 mL, 6.79 mmol) at −78 °C over a period of 15 min. After 5 min a further solution containing **2** (1.75 g, 6.79 mmol) in THF (20 mL) was added dropwise over a period of 30 min. Subsequently, the reaction mixture was stirred for 2 h at the same temperature before the cooling bath was removed. The reaction was quenched by addition of sat. aq. NH_4Cl-solution (60 mL) at ambient temperature and the molecular sieve was filtered off. The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried with Na_2SO_4. Removing of the solvent followed by column chromatography (methylene chloride/ethyl acetate 5:1) furnished **3** (2.77 mg, 4.97 mmol, 80%, anomeric mixture α:β, 1:5) as a colorless crystalline solid. R_f = 0.22–0.46 (methylene chloride/ethyl acetate 5:1).

3β*(major anomer): ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) = 5.04 (d, $J_{5,4}$ = 2.2 Hz, 1H, H-5), 4.82 (dd, $J_{9,8}$ = 5.7 Hz, $J_{9,10}$ = 3.5 Hz, 1H, H-9), 4.53 (d, $J_{8,9}$ = 5.9 Hz, 1H, H-8), 4.38–4.44 (m, 1H, H-11), 4.33–4.35 (m, 1H, H-4), 4.15 (dd, $J_{10,11}$ = 7.2 Hz, $J_{10,9}$ = 3.5 Hz, 1H, H-10), 4.07–4.11 (m, 1H, H-12a), 4.03 (dd, *J* = 8.7 Hz, *J* = 4.9 Hz, 1H, H-12b), 3.86–3.95 (m, 2H, H-1a, H-1b), 3.71–3.76 (m, 2H, H-2, H-3), 2.77 (s, 1H, OH), 1.50, 1.44, 1.42, 1.40, 1.38, 1.31 (6s, 18H, C(CH_3)$_2$), 0.87 (s, 9H, SiC(CH_3)$_3$), 0.07, 0.06 (2s, 6H,SiCH_3). ^{13}C-NMR (101 MHz, $CDCl_3$): δ(ppm) = 150.4 (C-6), 113.3, 109.1 (*C*(CH$_3$)$_2$), 104.3 (C-5), 103.4 (C-7), 99.4 (*C*(CH$_3$)$_2$), 86.7 (C-8), 80.0 (C-9), 79.4 (C-10), 73.2 (C-11), 72.9 (C-3), 70.2 (C-2), 68.2 (C-4), 66.7 (C-12), 61.7 (C-1), 28.9, 26.8, 25.8 (C(*C*H$_3$)$_2$), 25.7 (SiC(*C*H$_3$)$_3$), 25.4, 25.0, 19.1 (C(*C*H$_3$)$_2$), 18.1 (Si*C*(CH$_3$)$_3$), –4.4, –4.8 (Si*C*H$_3$).

3α*(minor anomer): ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) = 5.07 (d, $J_{5,4}$ = 2.1 Hz, 1H, H-5), 4.79 (dd, $J_{9,8}$ = 6.0 Hz, $J_{9,10}$ = 3.7 Hz, 1H, H-9), 4.62 (d, $J_{8,9}$ = 6.0 Hz, 1H, H-8), 4.34–4.35 (m, 2H, H-4, H-11), 4.10–4.11 (m, 1H, H-12a), 4.01–4.02 (m, 1H, H-12b), 3.85–3.88 (m, 2H, H-1a, H-1b, 3.76–3.80 (m, 3H, H-2, H-3, H-10), 2.77 (s, 1H, OH), 1.57, 1.49, 1.42, 1.40, 1.36 (5s, 18H, C(CH_3)$_2$), 0.88 (s, 9H, SiC(CH_3)$_3$), 0.08, 0.07 (2s, 6H, SiCH_3). ^{13}C-NMR (101 MHz, $CDCl_3$): δ(ppm) = 150.8 (C-6), 113.6, 109.3 (*C*(CH$_3$)$_2$), 103.1 (C-5), 100.6 (C-7), 99.6 (*C*(CH$_3$)$_2$), 80.7 (C-8), 80.0 (C-9), 78.6 (C-10), 73.2 (C-11), 72.8 (C-3), 70.3 (C-2), 67.8 (C-4), 67.2 (C-12), 61.7 (C-1), 28.9, 26.9, 25.9 (C(*C*H$_3$)$_2$), 25.8 (SiC(*C*H$_3$)$_3$), 25.2, 24.6, 19.0 (C(*C*H$_3$)$_2$), 18.2 (Si*C*(CH$_3$)$_3$), –4.4, –4.8 (Si*C*H$_3$). HRESIMS *m*/*z* 581.27570 (calcd for $C_{27}H_{46}O_{10}SiNa$, 581.27524); anal. C 58.37, H 8.21, calcd for $C_{27}H_{46}O_{10}Si$, C 58.04, H 8.39. *Anomers **3β** and **3α** could be interchanged

2,6-Anhydro-5-deoxy-7-O-acetyl-4-O-(tert-butyldimethylsilyl)-1,3:8,9:11,12-tri-O-isopropylidene-β-D-manno-D-lyxo-dodeco-6-enitol (**4a**)

A solution of **3** (300 mg, 0.537 mmol) and 4-dimethylaminopyridine (13 mg, 0.107 mmol) in triethylamine (7 mL) was treated with acetic anhydride (508 μL, 5.37 mmol) at 0 °C. After stirring for 12 h at ambient temperature until TLC indicated complete transformation of the starting material, the reaction mixture was diluted with ethyl acetate (20 mL). The organic phase was washed with 1 N hydrochloric acid (3 × 10 mL), sat. aq. NH_4Cl-solution (1 × 10 mL) and brine (1 × 10 mL). The solution was dried with Na_2SO_4, the solvent was removed and the crude product was purified by column chromatography (petroleum ether/ethyl acetate 5:1) to afford **4a** (309 mg, 0.515 mmol, 96%) as a colorless crystalline solid. R_f = 0.82 (methylene chloride/ethyl acetate 5:1). $[\alpha]_D^{20}$ = +64.3 (c = 1.0, $CHCl_3$). M.p. 52 °C (*n*-hexane). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.99 (d, $J_{5,4}$ = 2.2 Hz, 1H, H-5), 4.86 (dd, $J_{9,8}$ = 5.6 Hz, $J_{9,10}$ = 3.4 Hz, 1H, H-9), 4.69 (d, $J_{8,9}$ = 5.6 Hz, 1H, H-8), 4.42 (ddd, *J* = 8.3 Hz, *J* = 5.9 Hz, *J* = 3.9 Hz, 1H, H-11), 4.35 (dd, $J_{4,3}$ = 6.7 Hz, $J_{4,5}$ = 2.1 Hz, 1H, H-4), 4.09–4.15 (m, 1H, H-12a), 3.99–4.07 (m, 2H, H-10, H-12b), 3.80–3.89 (m, 2H, H-1aH-1b), 3.61–3.73 (m, 2H, H-2, H-3), 2.01 (s, 3H, COCH_3), 1.48, 1.47, 1.45, 1.37, 1.37, 1.33 (6s, 18H, C(CH_3)$_2$), 0.83 (s, 9H, SiC(CH_3)$_3$), 0.03, 0.03 (2s, 6H, SiCH_3).^{13}C-NMR (101 MHz, $CDCl_3$): δ(ppm) = 168.3 (CO), 146.9 (C-6), 113.9, 109.4 (*C*(CH$_3$)$_2$), 107.4 (C-7), 104.8 (C-5), 99.3 (*C*(CH$_3$)$_2$), 86.4 (C-8), 81.2 (C-10), 79.6 (C-9), 73.0 (C-3), 72.8 (C-11), 70.2 (C-2), 68.2 (C-4), 67.1 (C-12), 61.7 (C-1), 28.9, 27.0, 25.8 (C(*C*H$_3$)$_2$), 25.6 (SiC(*C*H$_3$)$_3$), 25.1, 25.1 (C(*C*H$_3$)$_2$), 21.5

($COCH_3$), 19.1 ($C(CH_3)_2$), 18.0 ($SiC(CH_3)_3$), –4.4, –4.9 ($SiCH_3$). HRESIMS *m*/*z* 623.28604 (calcd for $C_{29}H_{48}O_{11}SiNa$, 623.28581); anal. C 58.10, H 8.21, calcd for $C_{29}H_{48}O_{11}Si$, C 57.98, H 8.05.

2,6-Anhydro-5-deoxy-7-O-benzoyl-4-O-(tert-butyldimethylsilyl)-1,3:8,9:11,12-tri-O-isopropylidene-β-D-manno-D-lyxo-dodeco-6-enitol (**4b**)

A solution of **3** (930 mg, 1.67 mmol) and DMAP (41 mg, 0.333 mmol) in pyridine (15 mL) was treated with benzoyl chloride (1.92 mL, 16.7 mmol) at 0 °C. After stirring for 48 h at ambient temperature TLC indicated complete transformation of the starting material and the reaction mixture was diluted with ethyl acetate (60 mL). The organic layer was washed with 1 N hydrochloric acid (3 × 30 mL), sat. aq. $NaHCO_3$-solution (3 × 20 mL) and brine (1 × 20 mL). The solution was dried with Na_2SO_4, the solvent was removed and the crude product was purified by column chromatography (toluene/ethyl acetate, gradient: 100:1 – 20:1) to afford **4b** (749 mg, 1.13 mmol, 68%) as a colorless crystalline solid. R_f = 0.66 (toluene/ethyl acetate 4:1). $[\alpha]_D^{20}$ = +57.1(c = 1.0, $CHCl_3$). M.p. 58 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) = 7.90–8.02 (m, 2H, Ph), 7.52–7.62 (m, 1H, Ph), 7.39–7.48 (m, 2H, Ph), 5.11 (d, $J_{5,4}$ = 2.3 Hz, 1H, H-5), 4.90–5.01 (m, 2H, H-8, H-9), 4.47 (ddd, *J* = 8.2 Hz, *J* = 6.0 Hz, $J_{11,12b}$ = 4.0 Hz, 1H, H-11), 4.41 (dd, $J_{4,3}$ = 6.7 Hz, $J_{4,5}$ = 2.2 Hz, 1H, H-4), 4.08–4.17 (m, 2H, H-10, H-12a), 4.05 (dd, $J_{12b,12a}$ = 9.1 Hz, $J_{12b,11}$ = 4.0 Hz, 1H, H-12b), 3.66–3.84 (m, 4H, H-1a, H-1b, H-2, H-3), 1.52, 1.48, 1.42, 1.38, 1.37 (5s, 18H, $C(CH_3)_2$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.06, 0.06 (2s, 6H, $SiCH_3$).^{13}C-NMR (101 MHz, $CDCl_3$): δ(ppm) = 164.0 (CO), 147.3 (C-6), 133.4, 130.2, 129.9, 128.5 (Ph), 114.2, 109.6 ($C(CH_3)_2$), 108.2 (C-7), 105.1 (C-5), 99.5 ($C(CH_3)_2$), 86.7 (C-8), 81.8 (C-10), 80.0 (C-9), 73.3 (C-3), 73.0 (C-11), 70.4 (C-2), 68.5 (C-4), 67.3 (C-12), 61.8 (C-1), 29.1, 27.1, 26.0 ($C(CH_3)_2$), 25.8 ($SiC(CH_3)_3$), 25.4, 25.3, 19.3 ($C(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), –4.2, –4.7 ($SiCH_3$). HRESIMS *m*/*z* 685.30154 (calcd for $C_{34}H_{50}O_{11}SiNa$, 685.30146); anal. C 61.26, H 8.02, calcd for $C_{34}H_{50}O_{11}Si$, C 61.61, H 7.60.

General Procedure A for Desilylation of **4a** *and* **4b**

Tetra-*n*-butylammonium fluoride (1.0 M in THF, 1.5 eq.) was added to a solution of **4a** or **4b** (1.0 mmol) in THF (10 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirring was continued until complete conversion of the starting material was detected by TLC. Subsequently, the solution was diluted with CH_2Cl_2 (20 mL) and washed with brine (3 × 10 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic phases were dried with Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (petroleum ether/ethyl acetate 2:1 containing 0.5% Et_3N).

2,6-Anhydro-5-deoxy-7-O-acetyl-1,3:8,9:11,12-tri-O-isopropylidene-β-D-manno-D-lyxo-dodeco-6-enitol (**5a**)

Following general procedure A **5a** was obtained as a white amorphous solid and was prepared from **4a** in 71% yield stirring the reaction mixture for 20 h. R_f = 0.28 (petroleum ether/ethyl acetate 1:1). $[\alpha]_D^{20}$= +98.0 (c = 1.0, $CHCl_3$). M.p. 179 °C (*n*-hexane/ethyl acetate). ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) = 5.14 (d, $J_{5,6}$ = 2.2 Hz, 1H, H-5), 4.88 (dd, $J_{9,8}$ = 5.7 Hz, $J_{9,10}$ = 3.5 Hz, 1H, H-9), 4.71 (d, $J_{8,9}$ = 5.7 Hz, 1H, H-8), 4.37–4.45 (m, 2H, H-4, H-11), 4.01–4.12 (m, 3H, H-10, H-12a, H-12b), 3.85–3.94 (m, 2H, H-1a, H-1b), 3.68–3.80 (m, 2H, H-2, H-3), 2.02 (s, 3H, $COCH_3$), 1.53, 1.47, 1.45, 1.42, 1.37, 1.33 (6s, 18H, $C(CH_3)_2$). ^{13}C-NMR (101 MHz, $CDCl_3$): δ (ppm) = 168.2 (CO), 148.0 (C-6), 113.7, 109.4 ($C(CH_3)_2$), 107.1 (C-7), 102.9 (C-5), 99.7 ($C(CH_3)_2$), 86.3 (C-8), 81.5 (C-10), 79.6 (C-9), 73.2 (C-3), 72.8 (C-11), 69.9 (C-2), 67.8 (C-4), 67.0 (C-12), 61.5 (C-1), 28.9, 27.0, 25.8, 25.1, 24.9 ($C(CH_3)_2$), 21.6 ($COCH_3$), 19.2 ($C(CH_3)_2$). HRESIMS *m*/*z* 509.19928 (calcd for $C_{23}H_{34}O_{11}Na$, 509.19933); anal. C 56.57, H 7.17, calcd for $C_{23}H_{34}O_{11}$, C 56.78, H 7.04.

2,6-Anhydro-5-deoxy-7-O-benzoyl-1,3:8,9:11,12-tri-O-isopropylidene-β-D-manno-D-lyxo-dodeco-6-enitol (**5b**)

Following general procedure A **5b** was obtained as a colorless amorphous solid and was prepared from **4b** in 89% yield stirring the reaction mixture for 24 h. R_f = 0.37 (petroleum ether/ethyl acetate 1:1). $[\alpha]_D^{20}$ = +89.4 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) = 7.92–7.99 (m, 2H, Ph), 7.54–7.60 (m, 1H, Ph), 7.41–7.47 (m, 2H, Ph), 5.26 (d, $J_{5,4}$ = 2.2 Hz, 1H, H-5), 4.99 (dd, $J_{9,8}$ = 5.9 Hz,

$J_{9,10}$ = 3.6 Hz, 1H, H-9), 4.95 (d, $J_{8,9}$ = 5.9 Hz, 1H, H-8), 4.41–4.50 (m, 2H, H-4, H-11), 4.09–4.14 (m, 2H, H-10, H-12a), 4.04 (dd, *J* = 9.1 Hz, *J* = 4.2 Hz, 1H, H-12b), 3.72–3.88 (m, 4H, H-1a, H-1b, H-2, H-3), 2.11 (br. s., 1H, OH), 1.53, 1.52, 1.42, 1.41, 1.38, 1.36 (6 s, 18H, C(CH_3)$_2$).^{13}C-NMR (101 MHz, $CDCl_3$): δ(ppm) = 163.9 (CO), 148.4 (C-6), 133.5, 130.1, 129.9, 128.6 (Ph), 114.0, 109.6 (*C*(CH_3)$_2$), 107.9 (C-7), 103.2 (C-5), 99.9 (*C*(CH_3)$_2$), 86.6 (C-8), 82.0 (C-10), 79.9 (C-9), 73.4 (C-3), 73.0 (C-11), 70.2 (C-2), 68.1 (C-4), 67.2 (C-12), 61.6 (C-1), 29.1, 27.1, 26.0, 25.2, 25.1, 19.4 (C(CH_3)$_2$). HRESIMS *m*/*z* 571.21543 (calcd for $C_{28}H_{36}O_{11}Na$, 571.21498); anal. C 61.18, H 6.77, calcd for $C_{28}H_{36}O_{11}$, C 61.30, H 6.61.

General Procedure B for Epoxidation of **5a** *and* **5b** *and Further Rearrangement to the Oxetanes*

To a solution of *m*CPBA (2.5 eq.) in CH_2Cl_2 (10 mL) was added potassium fluoride (5 eq.) and the resulting suspension was stirred for 30 min at ambient temperature. A solution containing **5a** or **5b** (0.5 mmol) in CH_2Cl_2 (10 mL) was added in one portion and stirring was continued for 2 h (epoxidation). To enforce the rearrangement to the oxetanes the reaction mixture was stirred for 20 h, the white precipitate was filtered off and the solution was stirred for further 20 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$-solution (10 mL) and sat. aq. $Na_2S_2O_3$-solution (10 mL). Subsequently, the aqueous layer was extracted by CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried with Na_2SO_4, the solvent was removed and the crude product was purified by column chromatography.

5,6-Anhydro-7-O-acetyl-1,3:8,9:11,12-tri-O-isopropylidene-β-D-manno-β-D-manno-dodeco-6,7-diulo-2,6-pyranose-7,10-furanose (**6a**)

Following general procedure B a mixture of **6a** and **7a** (8:1) was obtained after quenching the reaction after 2 h as a white amorphous solid and was prepared from **5a** in 94% yield. A mixture of petroleum ether/ethyl acetate 3:1 containing 0.5% Et_3N was used as the eluent for column chromatography. R_f = 0.58 (petroleum ether/ethyl acetate 1:2). ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) = 4.96 (d, $J_{8,9}$ = 6.0 Hz, 1H, H-8), 4.91 (dd, $J_{9,8}$ = 6.0 Hz, $J_{9,10}$ = 3.9 Hz, 1H, H-9), 4.31–4.38 (m, 1H, H-11), 4.20 (dd, $J_{10,11}$ = 6.6 Hz, $J_{10,9}$ = 3.9 Hz, 1H, H-10), 3.85–4.06 (m, 5H, H-1a, H-3, H-4, H-12a, H-12b), 3.77 (dd, *J* = 10.7 Hz, *J* = 10.7 Hz, 1H, H-1b), 3.66 (d, $J_{5,4}$ = 2.4 Hz, 1H, H-5), 3.49 (ddd, *J* = 10.2 Hz, *J* = 10.2 Hz, *J* = 5.7 Hz, 1H, H-2), 2.38 (br. s., 1H, OH), 2.06 (s, 3H, COCH_3), 1.57, 1.48, 1.42, 1.39, 1.35, 1.33 (6s, 18H, C(CH_3)$_2$). ^{13}C-NMR (101 MHz, $CDCl_3$): δ(ppm) = 169.2 (CO), 114.2, 109.2 (*C*(CH_3)$_2$), 107.9 (C-7), 99.7 (*C*(CH_3)$_2$), 86.2 (C-8), 85.0 (C-6), 82.9 (C-10), 79.9 (C-9), 73.2 (C-11), 73.0 (C-3), 70.6 (C-2), 69.9 (C-4), 66.4, 61.7 (C-1), 57.3 (C-5), 29.1, 27.0, 25.6, 25.3, 24.6 (C(*C*H_3)$_2$), 21.9 (COCH_3), 19.3 (C(*C*H_3)$_2$). HRESIMS *m*/*z* 525.19448 (calcd for $C_{23}H_{34}O_{12}Na$, 525.19425).

5,6-Anhydro-7-O-benzoyl-1,3:8,9:11,12-tri-O-isopropylidene-β-D-manno-β-D-manno-dodeco-6,7-diulo-2,6-pyranose-7,10-furanose (**6b**)

Following general procedure B, a mixture of **6b** and **7b** (8:1) was obtained after quenching the reaction after 2 h as a white amorphous solid and was prepared from **5b** in 90% yield. A mixture of petroleum ether/ethyl acetate 3:1 containing 0.5% Et_3N was used as the eluent for column chromatography. R_f = 0.64 (petroleum ether/ethyl acetate 1:2). ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) = 7.92–7.99 (m, 2H, Ph), 7.59–7.63 (m, 1H, Ph), 7.45–7.50 (m, 2H, Ph), 5.18 (d, $J_{8,9}$ = 6.0 Hz, 1H, H-8), 5.03 (dd, $J_{9,8}$ = 6.1 Hz, $J_{9,10}$ = 4.0 Hz, 1H, H-9), 4.34–4.41 (m, 1H, H-11), 4.31 (dd, $J_{10,11}$ = 6.6 Hz, $J_{10,9}$ = 3.9 Hz, 1H, H-10), 4.13–4.18 (m, 1H, H-4), 4.03 (dd, *J* = 8.9 Hz, *J* = 6.2 Hz, 1H, H-12a), 3.91–3.99 (m, 2H, H-3, 12b), 3.73–3.83 (m, 3H, H-1a, H-1b, H-5), 3.54 (ddd, *J* = 10.0 Hz, *J* = 10.0 Hz, *J* = 6.0 Hz, 1H, H-2), 2.42 (br. s., 1H, OH), 1.62, 1.48, 1.39, 1.37, 1.34 (5s, 18H, C(CH_3)$_2$). ^{13}C-NMR (101 MHz, $CDCl_3$): δ(ppm) = 164.7 (CO), 133.8, 129.9, 129.8, 128.8 (Ph), 114.3, 109.2 (*C*(CH_3)$_2$), 108.5 (C-7), 99.7 (*C*(CH_3)$_2$), 86.4 (C-8), 85.3 (C-6), 83.2 (C-10), 80.0 (C-9), 73.2 (C-11), 73.0 (C-3), 70.7 (C-2), 69.9 (C-4), 66.4 (C-12), 61.6 (C-1), 57.4 (C-5), 29.0, 26.9, 25.6, 25.3, 24.6, 19.3 (C(*C*H_3)$_2$). HRESIMS *m*/*z* 587.21029 (calcd for $C_{28}H_{36}O_{12}Na$, 587.20990).

5,7-Anhydro-6-O-acetyl-1,3:8,9:11,12-tri-O-isopropylidene-β-D-manno-β-D-manno-dodeco-6,7-diulo-2,6-pyranose-7,10-furanose (**7a**)

Following general procedure B **7a** was obtained after quenching the reaction after 40 h as a white crystalline solid and was prepared from **5a** in 70% yield. A mixture of petroleum ether/ethyl acetate 2:1 was used as the eluent for column chromatography. Crystals from **7a** were grown by overlaying a saturated solution of **7a** in methylene chloride with *n*-heptane and slowly evaporating the methylene chloride. R_f = 0.51 (petroleum ether/ethyl acetate 1:2). $[\alpha]_D^{20}$ = +18.5 (c = 1.0, $CHCl_3$). M.p. 151 °C (*n*-hexane/ethyl acetate). ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) = 5.04 (d, $J_{8,9}$ = 5.6 Hz, 1H, H-8), 4.96 (d, $J_{4,5}$ = 4.9 Hz, 1H, H-5), 4.70 (dd, $J_{9,8}$ = 5.6 Hz, $J_{9,10}$ = 4.0 Hz, 1H, H-9), 4.37–4.46 (m, 1H, H-11), 4.00–4.13 (m, 3H, H-3, H-12a, H12b), 3.86–3.97 (m, 3H, H-1a, H-4, H-10), 3.80 (dd, *J* = 10.5 Hz, 1H, H-1b), 3.65–3.74 (m, 1H, H-2), 2.14 (d, $J_{OH,4}$ = 9.0 Hz, 1H, OH), 2.10 (s, 3H, $COCH_3$), 1.56, 1.55, 1.43, 1.43, 1.39, 1.36 (6s, 18H, $C(CH_3)_2$). ^{13}C-NMR (101 MHz, $CDCl_3$): δ(ppm) = 169.4 (*C*O), 114.2 ($C(CH_3)_2$), 112.9 (C-7), 109.5, 99.9 ($C(CH_3)_2$), 98.3 (C-6), 80.9 (C-5), 80.0 (C-10), 79.1 (C-8), 78.6 (C-9), 73.5 (C-11), 71.6 (C-3), 69.1 (C-2), 68.9 (C-4), 67.1 (C-12), 61.8 (C-1), 29.1, 27.1, 25.9, 25.8, 25.4 ($C(CH_3)_2$), 21.2 ($COCH_3$), 19.2 ($C(CH_3)_2$). HRESIMS *m*/*z* 525.19318 (calcd for $C_{23}H_{34}O_{12}Na$, 525.19425); anal. C 55.08, H 7.11, calcd for $C_{23}H_{34}O_{12}$, C 54.97, H 6.82.

5,7-Anhydro-6-O-benzoyl-1,3:8,9:11,12-tri-O-isopropylidene-β-D-manno-β-D-manno-dodeco-6,7-diulo-2,6-pyranose-7,10-furanose (**7b**)

Following general procedure B **7b** was obtained after quenching the reaction after 40 h as a white amorphous solid and was prepared from **5b** in 63% yield. A mixture of petroleum ether/ethyl acetate 2:1 was used as the eluent for column chromatography. R_f = 0.60 (petroleum ether/ethyl acetate 1:2). $[\alpha]_D^{20}$= +15.7 (c = 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, acetone-d_6): δ(ppm) = 8.04–8.10 (m, 2H, Ph), 7.68–7.74 (m, 1H, Ph), 7.53–7.59 (m, 2H, Ph), 5.16 (d, $J_{8,9}$ = 5.6 Hz, 1H, H-8), 5.10 (d, $J_{5,4}$ = 4.5 Hz, 1H, H-5), 4.82 (dd, $J_{9,8}$ = 5.6 Hz, $J_{9,10}$ = 3.7 Hz, 1H, H-9), 4.36 (ddd, *J* = 6.5 Hz, *J* = 6.5 Hz, *J* = 5.1 Hz, 1H, H-11), 4.15–4.26 (m, 2H, H-3, OH), 3.99–4.06 (m, 3H, H-4, H-10, H-12a), 3.80–3.97 (m, 4H, H-1a, H-1b, H-2, H-12b), 1.52, 1.51, 1.37, 1.35, 1.34, 1.28 (6s, 18H, $C(CH_3)_2$). ^{13}C-NMR (101 MHz, acetone-d_6): δ(ppm) = 165.7 (CO), 135.0, 130.8, 130.2, 129.7 (Ph), 114.2 ($C(CH_3)_2$), 113.5 (C-7), 109.5, 100.2 ($C(CH_3)_2$), 99.5 (C-6), 83.3 (C-5), 80.1 (C-10), 79.6 (C-9), 79.6 (C-8), 74.5 (C-11), 72.1 (C-3), 70.7 (C-2), 69.4 (C-4), 67.1 (C-12), 62.4 (C-1), 29.5, 27.2, 26.3, 26.2, 25.7, 19.3 ($C(CH_3)_2$). HRESIMS *m*/*z* 587.20977 (calcd for $C_{28}H_{36}O_{12}Na$, 587.20990); anal. C 59.64, H 6.86, calcd for $C_{28}H_{36}O_{12}$, C 59.57, H 6.43.

5,7-Anhydro-1,3:8,9:11,12-tri-O-isopropylidene-β-D-manno-β-D-manno-dodeco-6,7-diulo-2,6-pyranose-7,10-furanose (**8**)

From **7a**: **7a** (50 mg, 0.10 mmol) was dissolved in methanol (2 mL) and ammonia (7 N in methanol, 280 μL, 1.99 mmol) was added at ambient temperature. TLC indicated complete transformation of the starting material after 5 h and the volatile components were removed. Neat **8** (46 mg, 0.099 mmol, 99%) remained as a white crystalline solid.

From **7b**: **7b** (20 mg, 0.0354 mmol) was dissolved in methanol (1 mL) and ammonia (7 N in methanol, 101 μL, 0.708 mmol) was added at ambient temperature. TLC indicated complete transformation of the starting material after 5 h and the volatile components were removed. Subsequently, the crude product was purified by column chromatography (petroleum ether/ethyl acetate 1:2) and **8** (13 mg, 0.282 mmol, 80%) was isolated as a white crystalline solid.

R_f = 0.32 (petroleum ether/ethyl acetate 1:3). $[\alpha]_D^{20}$= +17.5 (c = 1.0, $CHCl_3$). M.p. 122 °C (*n*-hexane). ^{1}H-NMR (600 MHz, DMSO-d_6): δ(ppm) = 7.09 (s, 1H, OH-6), 5.16 (d, $J_{OH,4}$ = 5.7 Hz, 1H, OH-4), 4.75 (d, $J_{8,9}$ = 5.9 Hz, 1H, H-8), 4.57–4.63 (m, 2H, H-5, H-9), 4.22 (ddd, $J_{11,10}$ = 7.3 Hz, $J_{11,12a}$ = 6.4 Hz, $J_{11,12b}$ = 5.1, 1H, H-11), 4.01 (dd, $J_{12a,12b}$ = 8.4 Hz, $J_{12a,11}$ = 6.4 Hz, 1H, H-12a), 3.92 (dd, $J_{12b,12a}$ = 8.4 Hz, $J_{12b,11}$ = 5.1 Hz, 1H, H-12b), 3.78–3.85 (m, 2H, H-1a, H-3), 3.76 (dd, $J_{10,11}$ = 7.3 Hz, $J_{10,9}$ = 3.7 Hz, 1H, H-10), 3.68 (dd, $J_{1b,1a}$ = 10.5 Hz, $J_{1b,2}$ = 10.5 Hz, 1H, H-1b), 3.52 (ddd, *J* = 9.7 Hz, $J_{4,OH}$ = 5.1 Hz, *J* = 4.4 Hz, 1H, H-4), 3.40 (ddd, $J_{2,1b}$ = 9.9 Hz, *J* = 9.9 Hz, *J* = 5.8 Hz, 1H, H-2), 1.45, 1.39, 1.32, 1.31, 1.28, 1.26 (6s, 18H, $C(CH_3)_2$).^{13}C-NMR (101 MHz, DMSO-d_6): δ(ppm) = 112.5 (C-7), 112.3, 108.2, 98.8 ($C(CH_3)_2$), 97.4 (C-6), 83.9 (C-5), 78.2 (C-9), 77.0 (C-8), 76.9 (C-10), 72.7 (C-11), 71.1 (C-3), 67.8 (C-4), 66.8 (C-2), 66.1 (C-12), 61.1 (C-1), 28.9,26.6,

25.8, 25.5, 25.2, 19.0 (C(CH_3)$_2$). HRESIMS *m*/*z* 483.18377 (calcd for $C_{21}H_{32}O_{11}Na$, 483.18368); anal. C 54.58, H 7.41, calcd for $C_{21}H_{32}O_{11}$, C 54.78, H 7.00.

4. Conclusions

In summary, we have demonstrated that the stability of 2,5-anhydro sugars depends on their chemical environment. In the case of epoxide **6a** and **6b**, where an ester group is adjacent to the epoxide group, reversible rearrangements to highly annulated oxetane-bridged disaccharides **7a** and **7b** occur. In further studies, these compounds serve as precursors for the synthesis of symmetrical dodeco-6,7-diuloses.

Supplementary Materials: The following are available online at www.mdpi.com/link, ^{1}H-NMR and ^{13}C-NMR spectra of all compounds, H,H-NOESY-NMR spectra of compounds **4a** and **4b** and X-ray data of compounds **5a** and **7a**.

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